

## REMARKS

Claims 1-21, 23-25, 28-30, 33, 35-37, 40-50, 52-54, 107, 252-253, and 258-262 are pending in the application and have been examined and stand rejected. Claims 1, 54, 107, and 259-261 have been amended. No new matter has been introduced. Reconsideration and allowance of Claims 1-21, 23-25, 28-30, 33, 35-37, 40-50, 52-54, 107, 252-253, and 258-262 are respectfully requested.

### The Rejection of Claims 259-261 Under 35 U.S.C. § 112, Second Paragraph

Claims 259-261 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner has taken the position that Claims 259-261 are indefinite because all variables in the claims are not defined.

Claims 259-261 have been amended to specify that  $\gamma_1$  and  $\gamma_2$  represent quantitative trait random variables. Support for these amendments is found in the specification, published as WO 2004/013727, at page 93, line 18, to page 94, line 21. Accordingly, removal of this ground of rejection is respectfully requested.

### The Rejection of Claims 1, 2, 5-11, 42-44, 49, 50, 52, 53, 252, and 258 Under 35 U.S.C. § 102(b) as Being Anticipated by Aitman et al., *Nature Genetics* 21:76-83 (1999)

Claims 1, 2, 5-11, 42-44, 49, 50, 52, 53, 252, and 258 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Aitman et al., *Nature Genetics* 21:76-83 (1999). Applicants traverse this ground of rejection for at least the following reasons.

While not acquiescing to the Examiner's position, but in order to facilitate prosecution, Claim 1 has been amended to recite at step (A):

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(A) identifying an expression quantitative trait loci (eQTL) for said gene G using a first quantitative trait loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for said gene G as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for said gene G in an organism in said plurality of organisms, and wherein said first QTL analysis comprises (1) testing for linkages between the plurality of expression statistics for said gene G and a plurality of locations along a genetic map of the plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for said gene G using allelic association analysis . . . .

Support for this amendment is found in the specification as filed, published as WO 2004/013727; for example at page 88, line 27 to page 89, line 5.

The Examiner admits that Aitman et al. does not disclose determining whether a QTL maps to a plurality of positions in a genome. See final Office Action at page 9. Therefore, the claimed invention is novel over Aitman because the cited reference does not teach every element of the claimed invention. Removal of this ground of rejection is respectfully requested.

The Rejection of Claims 1 and 12-16 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Aitman et al.

Claims 1 and 12-16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Aitman et al. Applicants traverse this ground of rejection for at least the following reasons. Claim 1 has been amended at step A as indicated *supra*. As noted above, the Examiner admits that Aitman et al. does not disclose determining whether a QTL maps to a plurality of positions

in a genome. See final Office Action at page 9. It is further noted that Aitman et al. does not suggest or provide any motivation to practice the claimed invention, as amended.

Obviousness is determined by analyzing the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). *KSR* confirmed that the *Graham* factor analyses should be used in determining whether a claimed invention is obvious under 35 U.S.C. § 103(a). *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). The inquiry under *Graham* includes ascertaining the differences between the prior art and the claims at issue.

The Differences Between Aitman et al. and the Claimed Invention, as Amended

Contrary to the Examiner's assertion, Aitman et al. does not teach or suggest the identification of an expression quantitative trait loci (eQTL). As described in the instant specification at page 7, lines 20-24, an expression trait loci (eQTL) is identified using a plurality of expression statistics for a gene G, where each expression statistic in the plurality of expression statistics represents an expression value for gene G in an organism in a plurality of organisms.

Moreover, as acknowledged by the Examiner, Aitman et al. does not disclose testing for linkages between the plurality of expression statistics for gene G and a plurality of locations along a genetic map of the plurality of organisms, as required by Claims 1, as amended. Rather, Aitman et al. discloses the identification of a clinical quantitative trait loci (cQTL) for hypertension, hypertriglyceridaemia, reduced high density lipoprotein (HDL) phospholipid and metabolic defects on rat chromosome 4. See Aitman et al., page 76. Aitman et al. narrowed the clinical quantitative trait loci (cQTL) interval by phenotyping a new (SHRxWistar Kyoto (WKY) F2 cross (n=227) for insulin-mediated glucose uptake and catecholamine-mediated lipolysis and determined the genotypes of these animals for markers on chromosome 4. This work resulted in the identification of a cQTL with a lod score of 8.8 for defective catecholamine action and a lod score of 4.0 for defective insulin action that colocalizes with the microsatellite marker D4Bro1.

Aitman et al., pages 76-77. To further characterize the phenotype and to facilitate gene identification, Aitman created a congenic strain for chromosome 4 (SHR.4) in which the region of the chromosome 4 containing the microsatellite marker D4Bro1 was replaced with a corresponding region from Brown Norway (BN) genome, with the remainder of the genome derived from the SHR progenitor strain in which the cQTL was discovered. The SHR.4 strain showed partial correction of the insulin-mediated glucose uptake defect of the SHR strain and full correction of the isoproterenol-mediated lipolysis defect in the SHR strain. See Aitman et al. page 77. The only differential expression analysis described in Aitman et al. involved the comparison of hybridization signals between the SHR strain and insulin-sensitive control (BN and SHR.4 strains), resulting in the identification of three clones encoding rat Cd36 that showed reduced hybridization signals for SHR as compared to those of BN and SHR.4. It is noted that the differential expression experiments described in Aitman et al. did not identify a quantitative trait loci (QTL), much less an expression quantitative trait loci (eQTL) by (1) testing for linkages between the plurality of expression statistics for gene G and a plurality of locations along a genetic map of the plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for said gene G using allelic association analysis, as required by Claim 1, as amended.

The Differences Between the Teachings of Aitman et al. and Claim 1 Are Not Obvious Differences

As noted above, Aitman et al. does not teach or suggest the identification of an expression quantitative trait loci (eQTL). Because Aitman et al. does not teach or suggest testing for linkages between the plurality of expression statistics for gene G and a plurality of locations along a genetic map of the plurality of organisms, there would be no motivation or reasonable expectation for success for one to modify the teachings of Aitman et al. to arrive at the claimed

invention, as amended. Accordingly, applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness because the cited reference does not teach or suggest all the elements of the claimed invention, as amended. Accordingly, removal of this ground of rejection is respectfully requested.

The Rejection of Claims 1, 3, 4, 17-21, 23-25, 28-30, 33, 35-37, 40, 41, and 45-49 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Aitman et al. in View of Dominiczak et al., *Hypertension* 35(2):164-172 (2000)

Claims 1, 3, 4, 17-21, 23-25, 28-30, 33, 35-37, 40, 41, and 45-49 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Aitman et al. in view of Dominiczak et al., *Hypertension* 35(2):164-172 (2000). The Examiner characterizes Aitman et al. as discussed *supra*. The Examiner acknowledges that Aitman et al. does not disclose determining whether a QTL maps to a plurality of positions in a genome. The Examiner further acknowledges that Aitman et al. does not show mapping of a QTL with a precision of 1cM, or analysis of a human QTL. The Examiner further acknowledges that Aitman et al. does not show analysis of a trait affected by a plurality of mutations in different genes, or a high frequency of disease causing alleles, or non-Mendelian inheritance (limited penetrance) of a trait, or a trait that is hypertension. The Examiner cites Dominiczak et al. et al., *Hypertension* 35(2):165-172 as disclosing that human genes have been identified that contribute to hypertension with a lod score of greater than 2, and concludes that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the analysis of Aitman et al. by analyzing human QTL markers. Applicants traverse this ground of rejection for at least the following reasons.

It is noted that Claim 1, from which Claims 3, 4, 17-21, 23-30, 33, 35-37, 40-41, and 45-49 depend has been amended as described *supra*. As noted above, Aitman et al. does not teach or suggest the identification of an expression quantitative trait loci (eQTL). As described in the instant specification at page 7, lines 20-24, an expression trait loci (eQTL) is identified using a plurality of expression statistics for a gene G, where each expression statistic in the plurality of expression statistics represents an expression value for gene G in an organism in a plurality of organisms. It is further noted that Aitman et al. does not teach or suggest testing for linkages between a plurality of expression statistics for gene G and a plurality of locations along a genetic map of the plurality of organisms, as required by Claims 1, as amended.

The teachings of Dominiczak do not cure the deficiencies of Aitman et al. Dominiczak discloses the identification of clinical quantitative trait loci (cQTL) for hypertension using blood pressure subphenotypes and cardiovascular complications, such as left ventricular hypertrophy, kidney failure, and stroke. Dominiczak does not disclose, teach, suggest, or provide a reason to perform an eQTL analysis that uses a plurality of expression statistics for gene G as a quantitative trait. The QTL described by Dominiczak are cQTL because the blood pressure and cardiovascular phenotypes are phenotypic values for clinical traits T in an organism in a plurality of organisms rather than expression values for a gene G in organisms in a plurality of organisms. Moreover, Dominiczak does not teach or suggest testing for linkages between a plurality of expression statistics for gene G and a plurality of locations along a genetic map of the plurality of organisms, as required by Claims 1, as amended.

Accordingly, applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness because even if the cited references were to be combined, the cited references do not teach or suggest all the elements of the claimed invention, as amended. Accordingly, removal of this ground of rejection is respectfully requested.

The Rejection of Claims 54, 107, 253 and 262 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Aitman et al. in View of Manly et al., *Mammalian Genome* 10:327-334 (1999)

Claims 54, 107, 253, and 262 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Aitman et al. in view of Manly et al., *Mammalian Genome* 10:327-334 (1999). The Examiner characterizes Aitman et al. as discussed *supra*. The Examiner further notes that Aitman et al. discloses the use of a computer program termed MAPMAKER, however the Examiner acknowledges that Aitman et al. does not provide details of their genetic mapping calculations. As noted above, the Examiner further acknowledges that Aitman et al. does not disclose determining whether a QTL maps to a plurality of positions in a genome. The Examiner cites Manly et al. as disclosing the use of computer software for QTL analysis. The Examiner notes that Manly et al. discloses that two methods widely used are least squares regression and maximum likelihood estimation, as well as the use of interval mapping. The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a computer running the MAPMAKER program as disclosed in Aitman et al. because Manly et al. shows that MAPMAKER as well as other programs are useful to map QTL markers. Applicants traverse this ground of rejection for at least the following reasons.

Like Claim 1, from which Claims 253 and 262 depend, it is noted that independent Claims 54 and 107 have been amended at step (A) and now recite:

(A) identifying an expression quantitative trait loci (eQTL) for said gene G using a first quantitative trait loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for said gene G as a quantitative trait, wherein each expression statistic in said

plurality of expression statistics represents an expression value for said gene G in an organism in said plurality of organisms, and wherein said first QTL analysis comprises (1) testing for linkages between the plurality of expression statistics for said gene G and a plurality of locations along a genetic map of the plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for said gene G using allelic association analysis . . . .

Support for this amendment is found in the specification as filed, published as WO 2004/013727, for example at page 88, line 27, to page 89, line 5.

It is submitted that Claims 54 and 107 are each patentable over Aitman et al. for at least the same reasons that Claim 1 is patentable over Aitman et al. For example, as discussed above, Aitman et al. does not teach or suggest the identification of an expression quantitative trait loci (eQTL). As described in the instant specification at page 7, lines 20-24, an expression trait loci (eQTL) is identified using a plurality of expression statistics for a gene G, where each expression statistic in the plurality of expression statistics represents an expression value for gene G in an organism in a plurality of organisms. It is further noted that Aitman et al. does not teach or suggest testing for linkages between a plurality of expression statistics for gene G and a plurality of locations along a genetic map of the plurality of organisms, as required by Claims 1, 54, and 107, as amended.

The teachings of Manly et al. do not cure the deficiencies of Aitman et al. Manly et al. does not disclose the identification of an expression quantitative trait loci (eQTL). It is further noted that Manly et al. does not teach or suggest testing for linkages between a plurality of expression statistics for gene G and a plurality of locations along a genetic map of the plurality of organisms.



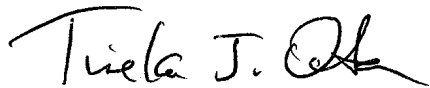
Accordingly, applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness because even if the cited references were to be combined, the cited references do not teach or suggest all the elements of Claims 1, 54, and 107, as amended. Accordingly, removal of this ground of rejection is respectfully requested.

#### CONCLUSION

Applicants believe that the pending claims are in condition for allowance. Reconsideration and allowance are respectfully requested. The Examiner is further requested to contact applicants' representative at 206.695.1655 to discuss any issues that may facilitate prosecution of this application

Respectfully submitted,

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